PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 12426030-E	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. **PCT/AU2004/000349**	International filing date *(day/month/year)* 19 March 2004	Priority date *(day/month/year)* 21 March 2003
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] C12Q 1/68		
Applicant THE MURDOCH CHILDRENS RESEARCH INSTITUTE et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand 17 January 2005	Date of completion of the report 14 February 2005
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/000349

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1 (b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☐ the international application as originally filed/furnished

☐ the description:

pages as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☐ the claims:

pages as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☐ the drawings:

pages as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**1-63**	**YES**
	Claims	**64**	**NO**
Inventive step (IS)	Claims	**3-5, 7, 15-18, 25-27, 29, 37-40, 48-51**	**YES**
	Claims	**1, 2, 6, 8-14, 19-24, 28, 30-36, 41-47, 52-64**	**NO**
Industrial applicability (IA)	Claims	**1-64**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

The present invention relates to methods for diagnosing, monitoring and treating pathogenic infection and other disease states in a subject. The diagnostic methods are based on assessment of levels of TLR-2 and/or TLR-4. The treatment methods are based on the administration of agents that modulate TLR-2 and/or TLR-4.

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1 Manigold et al (2003)

D2 Manigold et al (1999)

D3 O'Neill, L (2000)

D4 WO 2001/36488

D5 Paik et al (2003)

D6 Riordan et al (2003) Hepatology Vol 37(5): 1154-1164

D7 Riordan et al (2003) Gut Vol 52 No. Suppl. 1: A2

D8 Visvanathan et al (2003) Gut Vol 52 No. Suppl. 1: A53

D9 Visvanathan et al (2003) Gut Vol 52 No. Suppl. 1: A36

NOVELTY(N)

The claims are entitled to the priority that predates the publication date of D5 to D9. Unless the priority date of the invention as defined in the specification is challenged, the disclosures of D5 to D9 cannot be considered part of the prior art base for the consideration of novelty and inventive step.

Although the exact OPI date of the on-line version and print journal version of D1 has not been established by this ISA, D1 is considered relevant for the assessment of priority and inventive step.

(continued in supplemental box I)

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Independent claims 1, 12, 23, 34, 45, and 64, and dependent claims 5, 17, 27, 39 and 50 are not fully supported by the description. The specification only provides support for the association of HCV, HBV and cirrhosis with altered expression of TLR-2 and/or TLR-4. In contrast, the independent claims refer to any 'disease condition' and the dependent claims refer to hepatocellular carcinoma.

Present claims 45 to 64 refer to a large number of possible agents and their use. These agents are defined by a desirable property namely, antagonist/agonist or regulator of TLR-2 or TLR-4. The claims cover all substances and compounds having this property, whereas the application does not provide support within the meaning of Article 6 PCT for any specific example of such substances or compounds. Only agents and the use of agents that are direct derivatives of TLR-2 or TLR-4, such as specific antibodies or specific antisense molecules, appear to be supported by the description.

Supplemental Box I

In case the space in any of the preceding boxes is not sufficient.

Continuation of: V

Document 1 discloses TLR-2 and TLR-4 expression in peripheral blood monocytes (PMBC) and liver biopsy specimens obtained from subjects with liver cirrhosis. TLR-4 mRNA expression is significantly reduced in PMBC of subjects with alcoholic liver cirrhosis or viral liver cirrhosis, relative to healthy controls. TLR-2 mRNA expression is up-regulated in PMBC of subjects with high levels of endotoxin, whereas TLR-4 is down-regulated in subjects with low levels of endotoxin, compared with a control group. No significant differences were detected in TLR-2 and TLR-4 expression in biopsy samples from healthy subjects or subjects with liver cirrhosis. D1 does not explicitly teach a method of diagnosing disease or infection by assessing TLR-2 or TLR-4 expression, or treating disease or infection by modulating TLR-2 or TLR-4 levels, and therefore does not impact on the novelty of any of the claims.

Document 2 teaches TLR-2 mRNA expression is increased in subjects with cirrhosis. D2 does not explicitly teach a method of diagnosing disease or infection by assessing TLR-2 and does not impact on the novelty of any of the claims.

Document 3 reviews the role of toll-like receptors in inflammation and immunity, and does not impact on the novelty of any of the claims.

Document 4 discloses an antibody against human TLR-2 that inhibits TLR-2 activation, and the therapeutic use of the antibody in the treatment of bacterial infections mediated by the TLR-2 receptor. The antibody is considered an antagonist of TLR-2. Therefore D4 is prejudicial to the novelty of claim 64.

INVENTIVE STEP

Claims 1, 2, 4, 6, 10-14, 16, 21-24, 26, 28, 32-36, 38, 43-47, 49, 54-64 do not involve an inventive step in light of the teachings of D1. Given that D1 discloses levels of TLR-2 and TLR-4 are altered in subjects with cirrhosis, it would be obvious to the skilled person that determination and/or modulation of TLR-2 and/or TLR-4 levels would provide the basis for methods of diagnosing, prognosing and treating cirrhosis in a subject. Therefore, the above claims are considered to represent non-inventive applications of the disclosure of D1. However, D1 does not teach an association of HCV, HBV or HCC with altered TLR-2 or TLR-4 expression, and claims directed to such subject matter are inventive over D1.

Claims 1, 2, 4, 6, 10-14, 16, 21-24, 26, 28, 32-36, 38, 43-47, 49, 54-64 do not involve an inventive step in light of the teachings of D2. Given that D2 discloses levels of TLR-2 are altered in subjects with cirrhosis, it would be obvious to the skilled person that determination and/or modulation of TLR-2 would provide the basis for methods of diagnosing, prognosing and treating cirrhosis in a subject. Therefore, the above claims are considered to represent non-inventive applications of the disclosure of D2. However, D2 does not teach an association of HCV, HBV or HCC with altered TLR-2 expression, and claims directed to such subject matter are inventive over D2.

Claims 1, 2, 6, 8-14, 19-24, 28, 30-36, 41-46, 52-64 do not involve an inventive step in light of D3. The role of TLR-2 and TLR-4 in the development of host defence against various pathogens is well established. D3 is only one of many citations in the art which disclose that TLR-4 is required for LPS (endotoxin) responsiveness and TLR-2 is required for host defence against Gram-positive bacteria and fungi. Therefore, an inventive step is not acknowledged for the claims because they are considered to represent obvious methods and applications of the general principle that TLR-2 and TLR-4 are implicated in the host immune response to a wide range of pathogens. The specific selection of pathogens as recited in claims 8 and 9 is merely a subset of known pathogens that the skilled person would expect, in the light of what is known about TLR-2 and TLR-4, to induce a TLR-2 or TLR-4 mediated immune response. Consequently, an inventive step is not acknowledged for the claims.

(continued in supplemental box II)

Supplemental Box II

In case the space in any of the preceding boxes is not sufficient.

Continuation of: V

Claims 1, 2, 6, 8-14, 19-24, 28, 30-36, 41-46, 52-64 do not involve an inventive step in light of D4. In addition to an antibody to TLR-2, D4 teaches *Listeria*, *Mycobacterium avium*, *Staplococcus aures*, *Borrelia burgdorferi*, *Treponema pallidum* and *Mycobacterium fermantan* activate the host immune response via the TLR-2 receptor. Consequently the above claimed methods are considered obvious and non-inventive applications of the disclosure of D4.